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D-Cycloserine enhances both intrinsic excitability of CA1 hippocampal neurons and expression of activity-regulated cytoskeletal (Arc) protein

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HIGHLIGHTS

- D-Cyloserine modulates intrinsic excitability *via* Ca^{2+}-dependent K^+ conductances.
- D-Cycloserine decreases AHP duration and area 1 h after administration.
- D-Cycloserine decreases accommodation 1 h after administration.
- D-Cycloserine increases Arc protein expression 1 h after administration.

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ABSTRACT

The interaction of NMDA receptor (NMDAR) activation and other mechanisms regulating neuronal excitability have not been thoroughly described. While excess activation of NMDARs results in excitotoxicity, partial activation of NMDARs by D-cycloserine (DCS) is nootropic, enhancing both acquisition and extinction of memories. The mechanism by which DCS treatment enhances memory is unclear. NMDAR activation has been shown to increase expression of the activity-regulated cytoskeletal (Arc) protein associated with neural plasticity and enhanced memory. Enhanced memory is also associated with increases in neuronal intrinsic excitability, *i.e.* reductions in post-burst afterhyperpolarizations (AHPs) after acquisition of new tasks. Reductions in AHPs can occur when Ca^{2+} influx is reduced. This study aimed to determine if either if Arc expression, intrinsic excitability, or both were altered following systemic administration of a memory-enhancing dose of DCS, *i.e.* what form of plasticity would be exhibited. Both Arc protein expression and intrinsic excitability were enhanced in tissue prepared 1 h post-administration of a nootropic dose of DCS. Both mechanisms have been strongly associated with memory enhancement, but have not previously been demonstrated to change across the same time frame in the same preparation in response to DCS treatment.

1. Introduction

Considerable neuroscientific research has focused on regulation of neuronal excitability by targeting neuronal NMDA receptors (NMDARs) for development of memory enhancing (nootropic) drugs. While over-activation of NMDARs results in excitotoxicity through excessive influx of calcium ions (Ca^{2+}) [30], partial agonism of the glycine site through D-cycloserine (DCS) [11] activates NMDARs without major deleterious side effects [3,35] and has produced promising results in learning and memory studies.

Blockade of NMDARs with the antagonists APV or MK-801 blocks expression of activity regulated cytoskeletal protein, Arc [2]. Arc expression serves as a neural activity marker [9,13,15], being up-regulated in both long-term potentiation (LTP) and memory consolidation [8,13,14,27]. Conversely, Ca^{2+} influx activates several families of Ca^{2+}-dependent K^+ channels which, in turn, increases the amplitude and duration of afterhyperpolarizations (AHPs). In CA1 pyramidal neurons in particular, increased AHPs are associated

Abbreviations: DCS, D-cyloserine; NMDARs, NMDA receptors; Arc, activity regulated cytoskeletal protein; AHP, afterhyperpolarization; LTP, long-term potentiation; IEG, immediate-early gene.

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Table 1
DCS treatment did not significantly alter neuronal membrane input resistance, membrane sag in response to sustained −1.0 nA hyperpolarizing pulses, or resting membrane potential.

Group	*n* rats	*n* neurons	Input resistance (MΩ)	Sag (mV)	Resting potential (mV)
Control	10	14	43.1 ± 3.8	5.5 ± 0.5	−69.3 ± 0.6
DCS treated	5	7	45.8 ± 4.2	5.9 ± 1.0	−72.1 ± 0.9

with decreases in intrinsic excitability and impairments in learning and memory [5,20]. Reduced AHPs are associated with increased intrinsic excitability, and consistently associated with enhanced learning and memory in multiple species and in multiple learning tasks, from those requiring a single-trial for acquisition up through those requiring extensive training to reach criterion [5,6,20,22,33].

Blockade of NMDARs decreases Arc expression, a marker of activity associated with LTP and memory consolidation [2,8,9,13]. However, blockade of Ca^{2+} influx *via* NMDARs or voltage-gated channels can also enhance intrinsic excitability of neurons *via* reductions in Ca^{2+}-dependent AHPs [5,12]. DCS has been consistently shown to enhance both initial memory consolidation and subsequent memory extinction. Since the activation of NR1 glycine-binding subunits of NMDARs through administration of DCS enhances memories and since *de novo* activation of these glycine-binding sites increases Ca^{2+} influx, this study aims to directly assess both mechanisms to determine if these potentially discrepant activity-related events can account for the effects of DCS on memory enhancement.

DCS enhances acquisition, consolidation, and extinction of hippocampal-dependent memories in both animals and humans [25,28,31,32]. Doses of 5–20 mg/kg of DCS enhance acquisition of trace eyeblink conditioning [31,32], of non-spatial reference memory [1], and spatial list learning [34] among many others. DCS, which readily crosses the blood–brain barrier [4] has become a valuable adjunct therapy for treatment of post-traumatic stress and other memory problems resistant to extinction [3], so a better understanding of D-cycloserine's nootropic actions is needed.

In the current study, behaviorally naive rats were systemically administered a single memory enhancing dose of DCS *in vivo*. Brain tissue was collected 1 h later, so that measurements of plasticity in Arc protein expression or in post-burst AHPs could be taken at the same time point when both Arc protein expression and AHPs have been shown to be altered in the hippocampus following memory-related experiences [6,18].

2. Methods

2.1. Subjects

A total of 27 male Long Evans rats (250–350 g) were used in these experiments with 15 used for neurophysiological recordings and 12 for Western blotting analysis. Animals were cared for following the guidelines of the Institutional Animal Care and Use Committee (University of Texas at Dallas). They were housed communally with food and water available *ad libitum* and maintained on a 12 h light/dark cycle.

2.2. Drug treatment

A single dose of D-cycloserine (DCS; 6 mg/kg, i.p., pH 7.4) or saline vehicle (0.9% NaCl) was administered to male Long Evans rats. Rats were placed individually into holding cages after drug administration for 1 h. This dose of DCS has previously been shown to produce memory enhancement [31,32].

2.3. Tissue preparation for intracellular recordings

After 1 h, rats were anesthetized using isoflurane and quickly decapitated for brain removal. One h is within the time interval for maximal increases in Arc protein expression following learning or spatial exploration [9,12,23]. Brains were quickly removed and immersed in cooled, oxygenated (95% O_2: 5% CO_2) sucrose-aCSF (in mM: 124 sucrose; 3 KCl; 1.3 $MgSO_4$; 1.24 NaH_3PO_4; 2.4 $CaCl_2$; 26 $NaHCO_3$; 10 D-glucose; pH 7.4). Tissue was chilled for 4 min, blocked, and the hippocampus was sliced (400 μm thick) with a vibratome along the horizontal plane. Slices were equilibrated at room temperature (25 °C) in oxygenated (95% O_2: 5% CO_2) aCSF (in mM: 124 NaCl; 3 KCl; 1.3 $MgSO_4$; 1.24 NaH_3PO_4; 2.4 $CaCl_2$; 26 $NaHCO_3$; 10 D-glucose; pH 7.4) for >1 h before recordings were performed.

2.4. Current-clamp recordings with sharp electrodes

Sharp micropipettes were pulled from borocillate glass (30–80 MΩ, 3 M KCl) and used for intracellular recordings from pyramidal cells in the CA1. Slices were continuously perfused with aCSF (1.5 ml/min) at 31 °C and held between two nets. After intracellular penetration, all cells considered for inclusion had an input resistance of >35 MΩ, overshooting action potentials >80 mV, and a resting potential −70 ± 3 mV (see Table 1).

2.5. Neurophysiological data acquisition

Data were collected from all neurons with resting membrane potentials of −70 ± 3 mV, input resistance >30 MΩ, and action potential amplitudes >85 mV. AHPs were evoked by 100 ms depolarizing current injections sufficient to elicit four action potentials. Accommodation was tested using the same intensity current prolonged for 800 ms and measured as the number of spikes produced by this sustained current injection. Hyperpolarizing sag was determined by subtracting the maximal voltage deflection from baseline to steady-state voltage after a −1.0 nA step. *I–V* curves and input resistance (*IR*) were calculated by measuring the slope of the linear response to hyperpolarizing and subthreshold depolarizing 100 ms current pulses. The peak AHP was calculated as the difference between the resting membrane potential and the maximum negative membrane potential after the termination of the stimulus pulse. The time required for the membrane potential to return to the resting membrane potential for at least 10 ms after the termination of a stimulus pulse was determined as the AHP duration. The difference in potential before and after withdrawal of the recording electrode from the cell was used to measure the resting membrane potential.

2.6. Tissue preparation for Western blot analysis

Brains were submersed for 2 min in 2-methylbutane cooled by a dry ice/ethanol bath for flash freezing. 500 μm thick sections were taken along the coronal axis with a cryostat at the level of the dorsal hippocampus (−2.3 to −3.3 posterior from bregma) and tissue punches were taken with a tissue punch (1.22 mm in diameter). Tissue punches were collected in a sonication buffer containing 0.1 M phosphate buffer (10% glycerol, 20% protease inhibitor

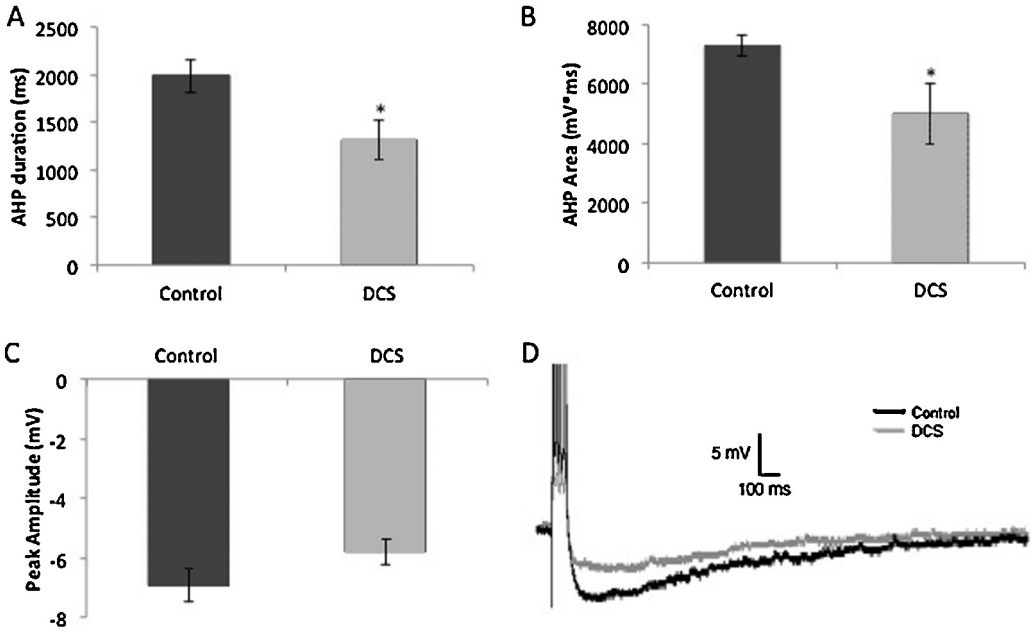

Fig. 1. Plasticity in AHPs 1 h following acute DCS administration. (A) DCS treatment (6 mg/kg, i.p., 7 CA1 neurons from 5 rats) significantly reduced the duration of post-burst AHPs compared to those from saline treated controls (14 CA1 neurons from 10 rats; * $p < 0.05$). (B) DCS treatment significantly reduced the area above the curve or the integrated area of the AHP compared to saline treated controls (* $p < 0.05$), but (C) did not significantly alter the peak amplitude of AHPs compared to those from saline treated controls. (D) Example post-burst AHP traces following four action potentials. Both duration and integrated area of the AHP were reduced in neurons from DCS treated rats compared to neurons from saline treated control rats. Values graphed are means ± SEM.

cocktail (Sigma-Aldrich), and 10% phosphotase inhibitory cocktail II (Sigma-Aldrich)) and sonicated for 1–3 s. Protein concentrations were determined using a Qubit fluorometer and Qubit protein assay kit (Invitrogen).

2.7. Western blot analysis

Approximately 15 μg of tissue was boiled in a solution with 25% LDS sample buffer and 10% reducing agent (Invitrogen) and run on a 4–12% bis–tris MIDI gel (Invitrogen). The gel was electroblotted to a nitrocellulose membrane using an iBlot dry blotting system (Invitrogen). Membranes were washed in tris-buffered saline (150 mM NaCl and 100 mM tris base; pH 7.5) and blocked in 5% milk overnight at 4 °C. Arc was probed for using Arc primary antibody diluted in blocking solution (Synaptic Systems; 1:6000) overnight at 4 °C followed by incubation in an HRP-conjugated secondary (goat–anti-rabbit; Abcam; 1:5454) for 1 h. Immunoreactivity was detected using chemiluminescence (ECL Western blot kit). Actin (Sigma-Aldrich; 1:1000) was used as a loading control. Each animal's lysate was run in its own lane on the same gel and the protein levels were quantified individually using a densitometry analysis with SCION ImageJ Software from NIH.

2.8. Statistical analysis

Statistical significance was determined in all measurements using a two-tailed unpaired two-sample *t*-test using StatView (SAS Institute). Raw data for neurophysiological data was collected using LabView (National Instruments) and processed using Igor (Wavemeterics).

3. Results

3.1. Effects on intrinsic excitability

Intracellular current clamp recordings were made from a total of 21 stable and healthy CA1 pyramidal neurons from 15 rats: 14 CA1 neurons from 10 control rats, and 7 CA1 neurons from 5 rats acutely treated with DCS.

Systemic administration of a memory enhancing dose of DCS (6 mg/kg, i.p.) [31,32] 1 h prior to slice preparation increased intrinsic excitability in dorsal CA1 pyramidal neurons compared to those from saline treated controls (Figs. 1 and 2). Specifically, acute DCS treatment significantly decreased the duration of post-burst AHPs by about 33% ($t(89) = 3.226$, $p < 0.01$; Fig. 1A and D). Acute DCS treatment also significantly decreased the area above the curve (the integrated area) of AHPs by about 31% ($t(89) = 2.208$, $p < 0.05$; Fig. 1C and D). Peak AHP amplitudes were not significantly altered when comparing between neurons from saline and DCS treated animals ($t(89) = 1.222$, $p = 0.225$; Fig. 1B), suggesting that faster components of post-burst AHPs were unaffected by DCS treatment.

Reductions in AHP duration and area were accompanied by decreases in spike-frequency accommodation. A significant increase (26%, from 8.9 ± 0.2 for controls to 11.3 ± 0.5 for DCS) in the number of spikes was produced in response to a sustained depolarizing stimulus ($t(89) = -3.067$, $p < 0.01$; Fig. 2A and B) by neurons from rats treated with DCS compared to controls. Previous studies have shown that learning-related reductions in hippocampal pyramidal neuron AHPs in both CA1 and CA3 are accompanied by reductions in spike-frequency accommodation as well [5,22,24,33].

DCS administration did not alter other membrane properties measured in CA1 pyramidal neurons, including input resistance and resting membrane potential (Table 1); this lack of non-specific membrane effects is consistent with previous findings for other nootropic compounds affecting AHPs [5,21]. No prior published studies have assessed the effects of DCS on post-burst AHPs.

3.2. Effects on Arc protein expression

Western blot analyses were carried out on dorsal hippocampal tissue samples from a total of 12 rats, 6 acutely treated with DCS and 6 controls to assess DCS induced changes in Arc protein expression.

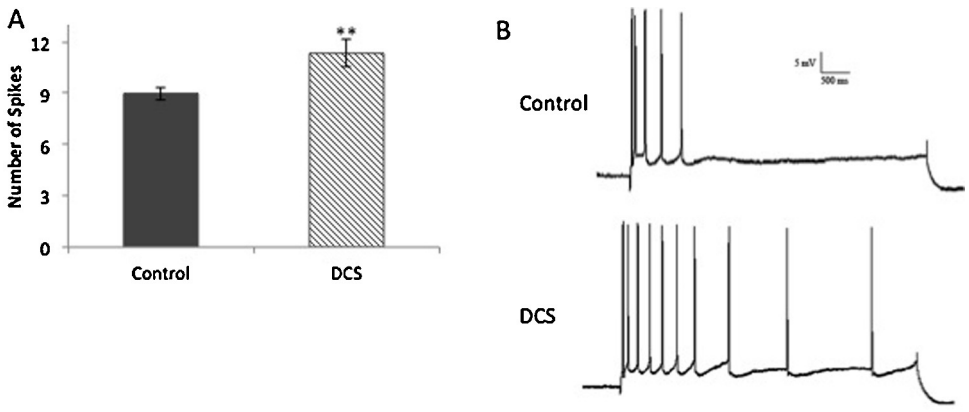

Fig. 2. Plasticity in accommodation 1 h following acute DCS administration. (A) DCS treatment (6 mg/kg, i.p., tested on 7 CA1 neurons from 5 rats) significantly increased the number of spikes in response to an 800 ms depolarizing stimulus pulse compared to response of neurons from saline treated controls (14 CA1 neurons from 10 rats; ** $p < 0.01$). (B) Example accommodation traces from saline treated controls and DCS treated rats. Neurons from DCS treated rats had decreased accommodation as seen by an increase in the number of spikes in response to a sustained depolarizing stimulus pulse compared to neurons from saline treated controls. Values graphed are means ± SEM.

In addition to measuring plasticity in intrinsic excitability of CA1 neurons, changes in expression of Arc, an immediate-early gene (IEG) product and marker of neuronal excitability [18,19], were measured at the same time point, 1 h post-DCS administration. DCS significantly increased Arc protein expression in the CA1 region of dorsal hippocampus 1 h after DCS administration, nearly doubling Arc expression compared to controls ($t(10) = -3.389$, $p < 0.01$). No prior published studies have assessed the effects of DCS on Arc protein expression.

4. Discussion

While DCS, a partial NMDAR agonist, enhances memory consolidation and extinction in rats and in humans [25,28,31,32], no prior studies investigated whether DCS treatment *in vivo* affects expression of Arc or regulation of intrinsic excitability. One hour after acute administration of DCS, both Arc protein expression (Fig. 3) and intrinsic neuronal excitability (Fig. 1, reductions in the post-burst AHP; and Fig. 2, reductions in accommodation) were significantly increased in hippocampal CA1 neurons. Both behavioral and neurophysiological effects of DCS *in vivo* are blocked by APV or MK-801, specific antagonists that prevent activation of NMDARs [3,11,16,19,23,36]. DCS directly competes with the NR1 subunit antagonists HA-966 [7,16,17,36] and 5,7-dichlorokynurenate [29], evidence for the specificity of DCS effects being mediated *via* binding to NR1 subunits of NMDARs. The regulation of Ca^{2+} influx through NMDARs is critical for consolidation [17,19,23,25,31,32] and extinction [3,16,28,35] of memory. In the hippocampus and other forebrain regions, both increases in Arc protein expression [8,10,14,18,27,34] and increases in neuronal excitability (reductions in post-burst AHPs) [5,6,20–22,24,33] have been extensively studied as mechanisms underlying memory, but it is notable that no prior studies looked for a relationship between them. Our findings will lead to further work, assessing plasticity of IEGs and their potential links to intrinsic excitability.

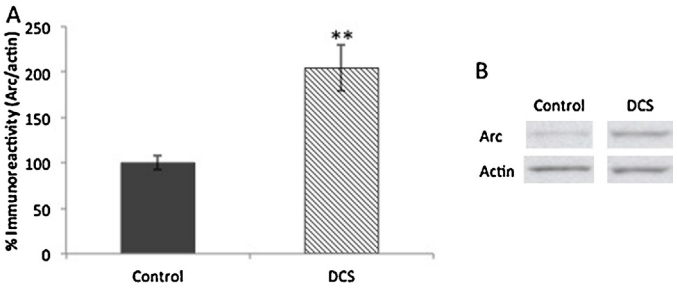

Fig. 3. Alterations in Arc protein expression 1 h following DCS administration. (A) DCS treatment ($n = 6$) significantly increased expression of Arc protein in the dorsal hippocampus compared to saline treated controls ($n = 6$; ** $p < 0.01$). (B) Example Western blots of Arc protein expression from the dorsal hippocampus of control and DCS treated animals, compared to actin, a cytoskeletal protein that is not regulated by calcium entry. Values graphed are means ± SEM.

NMDARs activate signaling cascades increasing expression of Arc protein, an activity marker associated with enhanced memory consolidation [2,8,11,20]. Prior studies found enhanced expression of Arc protein in the hippocampal CA1 region 1 h after nootropic (memory enhancing) administration of beta adrenergic agonists or of cortisol, with significant increases observed in Western blots from homogenized tissue [10,18,19]. Parallel Western and immunohistochemical analyses also demonstrated that these changes were generalized, with Arc expression increased robustly throughout pyramidal neuron populations in dorsal CA1 [18], not limited to a small subset of neurons.

Conversely, Ca^{2+} influx activates Ca^{2+}-dependent K^+ channels that increase AHPs, and increases in AHPs are associated with impaired memory consolidation and reduced pyramidal neuron intrinsic excitability [5,6,20,22,33]. The DCS-induced AHP reductions observed here occurred in all CA1 pyramidal neurons tested, along with reductions in spike frequency accommodation. While decreased spike-frequency accommodation is not always correlated with reduced post-burst AHPs, prior studies have shown that learning-related reductions CA1 and CA3 pyramidal neuron AHPs are usually accompanied by reductions in accommodation [5,6,22,24,33]. DCS in the present study produced coupled effects.

The increase in intrinsic excitability observed here is inconsistent with a reduction in Ca^{2+} influx, which would have precluded an increase in Arc expression. Instead, these changes in intrinsic excitability are consistent with PKA-mediated phosphorylation of Ca^{2+}-dependent K^+ channels underlying the slow components of the AHP [24,26], and enhanced PKA-mediated activity has also been associated with enhanced Arc expression [10,18,19]. Additional studies are needed to determine the specific mechanisms involved.

The current study assessed potential discrepancies in Ca^{2+} mediated memory enhancements by assessing two forms of plasticity at the same time point (1 h after an acute systemic dose of DCS), an activity-related IEG product and neurophysiological measures of intrinsic excitability: both were significantly enhanced. The interaction of DCS with NMDARs in dorsal hippocampus is sufficient to downregulate Ca^{2+}-dependent K^+ channel activity underlying the AHP while also enhancing Arc expression.

5. Conclusions

Acute systemic administration of a nootropic dose of D-cycloserine increased intrinsic neuronal excitability (reduced AHPs and accommodation) and increased Arc protein expression 1 h later in CA1 of hippocampus. Both mechanisms are strongly associated with memory enhancement, but had not previously been demonstrated as occurring together within the same time frame.

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